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Angiogenesis in glioblastoma: just another moving target?

Inhibition of angiogenesis as a concept experienced a renaissance in neuro-oncology in 2009. Based on encouraging phase II data suggesting increased response rates and improved quality of life, including a corticosteroid-sparing effect (Friedman *et al.*, 2009; Kreisl *et al.*, 2009), bevacizumab—an antibody that targets vascular endothelial-derived growth factor (VEGF)—was approved for the treatment of recurrent glioblastoma in the US and, for example, in Switzerland; but not throughout the European Union (Weller and Stupp, 2009). Further, the results of a 2:1:2 randomized trial comparing the VEGF receptor antagonist, cediranib (Batchelor *et al.*, 2007), with the alkylating agent lomustine, and the combination of cediranib and lomustine in patients with recurrent glioblastoma are to be presented at the American Society of Clinical Oncology meeting in June 2010. Finally, not only bevacizumab (and probably soon cediranib, too), but also another anti-angiogenic agent, the integrin antagonist cilengitide, are currently being evaluated in registration trials for patients with newly diagnosed glioblastoma (Stupp *et al.*, 2010).

Theoretical support for the therapeutic approach of angiogenesis inhibition in glioblastoma stems from the idea that the endothelial cell is the only stable, reliable element in an increasingly heterogeneous and chaotic tumour microenvironment. Genetic instability of glioma cells might drive rapid selection processes resulting in the generation of multiple and diverse resistant tumour cell clones. In contrast, it has commonly been assumed that (true) endothelial cells, which are non-neoplastic host cells recruited by the growing tumours, would be resistant to the development of resistance, because of their stable genetic phenotype. Yet, clinical experience has already taught us that such views are over-simplified.

First, not all vessel formation in glioma depends on VEGF. This is apparent from the rate of responding patients defined by classical neuroradiological outcome criteria of 30–50% (Batchelor *et al.*, 2007; Friedman *et al.*, 2009; Kreisl *et al.*, 2009). Whilst these data should be welcomed as promising, it must not escape our notice that at least half of glioblastomas do quite well in the presence of bevacizumab or cediranib, indicating that not all glioblastoma-related

angiogenesis is strictly dependent on VEGF. Second, the responses to anti-angiogenic agents targeting VEGF are commonly transient, suggesting that there are effective escape mechanisms for blood vessel formation, contradicting the wishful thinking of endothelial resistance to the development of resistance to targeted anti-angiogenic therapy. In fact, numerous other molecules, including other VEGF-family members as well as placenta-derived, hepatocyte and fibroblast growth factor, are implicated in the primary or acquired resistance to VEGF-antagonistic treatments.

Against this background, in the current issue of *Brain*, El Hallani *et al.* (2010) address a largely neglected mechanism by which gliomas maintain vascular perfusion—the formation of vessel-like structures by the tumour cells themselves, referred to as 'vasculogenic mimicry of the tubular type'. They identify a subset of glioblastomas characterized by 'blood vessels' that are lined by non-endothelial cells. This interpretation is based on the presence of collagen IV, a marker of blood vessel basement membranes, in the absence of the expression of CD34, a universal marker for endothelial cells. To support the idea that the vessel-lining cells are tumour cells, the authors demonstrate the amplification of epidermal growth factor receptor (EGFR) in these cells, in a tumour known to harbour the molecular phenotype of EGFR amplification. Some of the tumour cells express smooth muscle actin, indicating that these have trans-differentiated into vascular smooth muscle-like cells. Intriguingly, the authors provide one example of a tissue section where there appears to be an anastomosis between an endothelially lined and a tumour-derived 'vessel'. Finally, the authors analyse the subpopulation of glioma-initiating cells by CD133 sorting from two tumours, one with and one without putative tumour-derived blood vessels. CD133+ cells from the former tumour generate vessel-like structures in tube formation assays, whereas the latter do not. An expression of endothelium-associated genes was observed in both populations of glioma-initiating cells. These observations lead the authors to propose that the subpopulation of glioma-initiating cells may even possess the plasticity to form blood vessels. Taken as a whole, this study indicates that some glioblastomas may grow in

the absence of endothelial cell recruitment, suggesting that they may exhibit primary refractoriness to therapeutic approaches targeting VEGF. Clearly, further studies are needed to clarify the overall frequency of this phenotype and its contribution to the perfusion of glioblastomas in a larger sample of tumours.

The introduction of novel anti-angiogenic agents has already imposed new challenges on clinical neuro-oncologists, some of which have been faced and almost solved whereas others require new approaches. Thus, the response criteria devised by Macdonald and colleagues (1990) required modification in order to rely less on contrast enhancement, to include the necessity for confirmation of the response and to consider tumour extensions on T₂-weighted magnetic resonance imaging (Van den Bent *et al.*, 2009). The latter became necessary when it was recognized that some patients treated with bevacizumab exhibit altered patterns of recurrence reminiscent of gliomatosis cerebri, attributed to a change from vessel- and VEGF-dependent to growth that is independent of each (Norden *et al.*, 2008). Future clinical trials will aim to identify prospective biomarkers associated with response or lack of response to anti-angiogenic agents. But it is now clear that such analyses should start with a careful neuropathological and neuroradiological characterization of the pre-treatment vascularization of these tumours.

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